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(54) Title: USE OF FK506 AND ANALOGUES FOR TREATING ALLERGIC DISEASES

(57) Abstract: The present invention provides, in the treatment of allergic diseases using an interleukin 2 inhibitor, particularly a macrolide compound such as FK506, a method of treating an allergic disease, which includes setting a leading period for pre-administration of an interleukin 2 inhibitor.

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DESCRIPTION

USE OF FK506 AND ANALOGUES FOR TREATING ALLERGIC DISEASES

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a method for treating allergic diseases.

BACKGROUND ART

When a foreign matter invades the body, an antibody or sensitized lymphocyte is generated by an immune response. The antibody or sensitized lymphocyte reacts with the foreign matter when it invades again, whereby the foreign matter is removed or attenuated. This is the so-called "immunity". When the reaction proceeds inversely to damage the body, it is called an "allergy".

An allergic reaction was classified into IgE dependent anaphylactic type (I type), cytotoxic type (II type), immune complex type (III type), and cellular immunity type (IV type) by Coombs and Gell (1963) based on the mechanism of immune reaction. It is considered that these reaction types are involved in a complicated manner to cause allergic diseases in the living body.

The I type allergy is a general name for hypersensitiveness caused by the reaction with IgE antibody upon contact with an allergen, and this type is also called an atopic disease. For example, bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy, and a part of drug allergy fall under the atopic diseases.

In the meantime, a macrolide compound, such as FK506, and cyclosporins are known to be effective for the treatment of allergic diseases such as allergic conjunctivitis, spring catarrh, atopic dermatitis and the like (WO 92/19278 etc.).

DISCLOSURE OF THE INVENTION

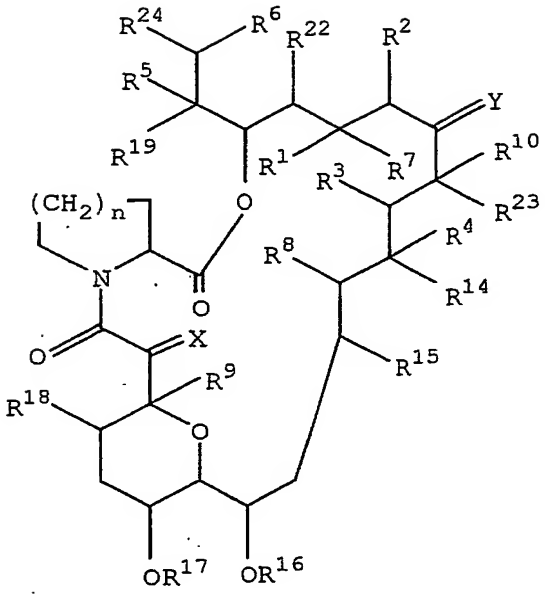
The present inventor has conducted intensive studies and surprisingly found that, in the treatment of allergic diseases using an interleukin 2 (hereinafter sometimes referred to simply as IL-2) inhibitor, expression of the effect is drastically increased by setting a leading period for pre-administration of an IL-2 inhibitor, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

(1) A pharmaceutical agent for pre-administration, which comprises an interleukin 2 inhibitor (IL-2 inhibitor) as an active ingredient, and which is used for treating an allergic disease, wherein the treatment includes a leading period for pre-administration of the IL-2 inhibitor to a subject in need of the treatment of allergic disease, and administration of an effective amount of an IL-2 inhibitor.

(2) The pharmaceutical agent of (1), wherein the IL-2 inhibitor is a macrolide compound or a cyclosporin.

(3) The pharmaceutical agent of (2), wherein the macrolide compound is a tricyclo compound (I) of the following formula (hereinafter sometimes referred to simply as tricyclo compound (I));



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pairs;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2.

In addition to the meaning noted above, Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy, or a pharmaceutically acceptable salt thereof.

(4) The pharmaceutical agent of (2) or (3), wherein the macrolide compound is FK506.

(5) The pharmaceutical agent of (1), wherein the IL-2 inhibitor is a preparation for local administration, especially a preparation for local administration to the eye or the nose.

(6) The pharmaceutical agent of (1), wherein the allergic disease is allergic conjunctivitis.

(7) The pharmaceutical agent of (1), wherein the allergic disease is seasonal allergic disease, especially seasonal allergic conjunctivitis.

(8) A pharmaceutical composition for pre-administration, which comprises an IL-2 inhibitor as an active ingredient and a pharmaceutically acceptable carrier, and which is used for treating an allergic disease, wherein the treatment includes a leading period for pre-administration of the IL-2 inhibitor to a subject in need of the treatment of allergic disease, and administration of an effective amount of an IL-2 inhibitor.

(9) The pharmaceutical composition of (8), wherein the IL-2 inhibitor is a macrolide compound or a cyclosporin.

(10) The pharmaceutical composition of (9), wherein the macrolide compound is a tricyclo compound (I), or a pharmaceutically acceptable salt thereof.

(11) The pharmaceutical composition of (9) or (10), wherein the macrolide compound is FK506.

(12) The pharmaceutical composition of (8), wherein the IL-2 inhibitor is a preparation for local administration, especially a preparation for local administration to the eye or the nose.

(13) The pharmaceutical composition of (8), wherein the allergic disease is allergic conjunctivitis.

(14) The pharmaceutical composition of (8), wherein the allergic disease is seasonal allergic disease, especially seasonal allergic conjunctivitis.

(15) A method for treating an allergic disease, which comprises pre-administering an IL-2 inhibitor for a leading period and then administering an effective amount of an IL-2 inhibitor to a subject in need of a treatment of an allergic disease.

(16) The method of (15), wherein the IL-2 inhibitor is a macrolide compound or a cyclosporin.

(17) The method of (16), wherein the macrolide compound is a tricyclo compound (I), or a pharmaceutically acceptable salt thereof.

(18) The method of (16) or (17), wherein the macrolide compound is FK506.

(19) The method of (15), wherein the IL-2 inhibitor is a preparation for local administration, especially a preparation for local administration to the eye or to the nose.

(20) The method of (15), wherein the allergic disease is

allergic conjunctivitis.

(21) The method of (15), wherein the allergic disease is a seasonal allergic disease, especially seasonal allergic conjunctivitis.

(22) Use of an IL-2 inhibitor for the production of a pharmaceutical composition for pre-administration, which comprises the IL-2 inhibitor as an active ingredient and a pharmaceutically acceptable carrier, and which is used for treating an allergic disease, wherein the treatment includes a leading period for pre-administration of the IL-2 inhibitor to a subject in need of the treatment of allergic disease, and administration of an effective amount of an IL-2 inhibitor.

(23) The use of (22), wherein the IL-2 inhibitor is a macrolide compound or a cyclosporin.

(24) The use of (23), wherein the macrolide compound is a tricyclo compound (I), or a pharmaceutically acceptable salt thereof.

(25) The use of (23) or (24), wherein the macrolide compound is FK506.

(26) The use of (22), wherein the IL-2 inhibitor is a preparation for local administration, especially a preparation for local administration to the eye or the nose.

(27) The use of (22), wherein the allergic disease is allergic conjunctivitis.

(28) The use of (22), wherein the allergic disease is seasonal allergic disease, especially seasonal allergic conjunctivitis.

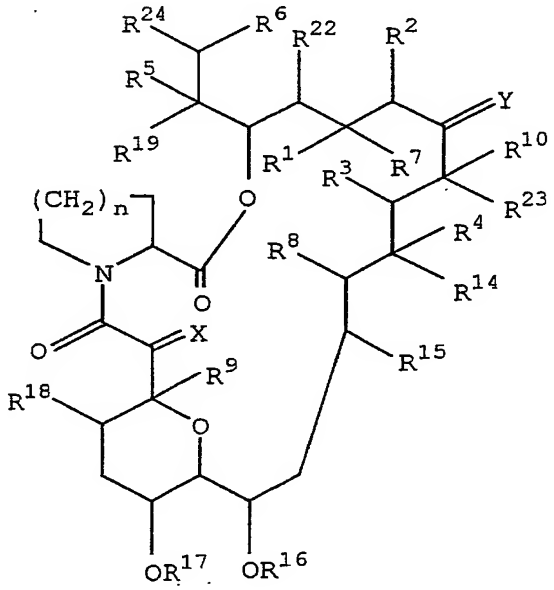
(29) A commercial package comprising the pharmaceutical composition of any of the above-mentioned (8) to (14) and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should

be used for pre-administration for treating allergic diseases, wherein the treatment includes a leading period for pre-administration of the IL-2 inhibitor to a subject in need of the treatment of allergic disease, and administration of an effective amount of an IL-2 inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

The IL-2 inhibitor to be used in the present invention is not particularly limited and may be any as long as it has an IL-2 inhibitory activity. One example thereof is an IL-2 production inhibitor. Another example is an IL-2 signal transduction inhibitor. Preferable examples thereof include macrolide compounds such as FK506, Ascomycin derivative, Rapamycin derivative and the like, and cyclosporins and the like.

Specific examples of macrolide compound include tricyclo compound (I) of the following formula and a pharmaceutically acceptable salt thereof.



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is

optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pairs;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2.

In addition to the meaning noted above, Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy.

Preferable R^{24} is, for example, cyclo(C_5 - C_7)alkyl optionally having suitable substituent, such as the following.

(a) 3,4-dioxocyclohexyl,

(b) 3-R^{20}-4-R^{21}-cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and

R^{21} is hydroxy, -OCN, alkyloxy, heteroaryloxy optionally having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired or protected amino, and R^{26} is hydrogen atom or methyl) or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring, and

(c) cyclopentyl wherein cyclopentyl is substituted by methoxymethyl, protected hydroxymethyl where desired, acyloxymethyl (wherein acyl moiety is optionally quaternized dimethylamino where desired or optionally esterified carboxy), one or more optionally protected amino and/or hydroxy, or aminooxalyloxymethyl. Preferable example includes 2-formyl-cyclopentyl.

The definition of each symbol used in the formula (I), specific examples thereof and preferable embodiments thereof are explained in detail in the following.

"Lower" means that a group has 1 to 6 carbon atoms unless otherwise indicated.

Preferable examples of the alkyl moiety of "alkyl" and "alkyloxy" include linear or branched aliphatic hydrocarbon residue, such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl and the like).

Preferable examples of "alkenyl" include linear or branched aliphatic hydrocarbon residue having one double bond, such as lower alkenyl (e.g., vinyl, propenyl (e.g., allyl and the like), butenyl, methylpropenyl, pentenyl, hexenyl and the like).

Preferable examples of "aryl" include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl and the like.

Preferable examples of the protective group for "protected hydroxy" and "protected amino" include 1-(lower alkylthio)(lower)alkyl such as lower alkylthiomethyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl and the like), with more preference given to C_1 - C_4 alkylthiomethyl and most preference given to methylthiomethyl;

tri-substituted silyl such as tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl dimethylsilyl, tri-tert-butylsilyl and the like), and lower alkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl and the like), with more preference given to tri(C_1 - C_4)alkylsilyl and C_1 - C_4 alkyldiphenylsilyl, and most prefererence given to tert-butyl-dimethylsilyl, tert-butyldiphenylsilyl;

acyl such as aliphatic acyl, aromatic acyl and aliphatic acyl substituted by aromatic group, which are derived from carboxylic acid, sulfonic acid and carbamic acid; and the like.

The aliphatic acyl is exemplified by lower alkanoyl optionally having one or more suitable substituent(s) (e.g., carboxy) such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl and the like;

cyclo(lower)alkyloxy(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyl) such as cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl,

mentyloxyacetyl, mentyloxypropionyl, mentyloxybutyryl, mentyloxypentanoyl, mentyloxyhexanoyl and the like,

camphorsulfonyl;

lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy, protected carboxy and the like, such as carboxy(lower)alkylcarbamoyl (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl) and

tri(lower)alkylsilyl(lower)alkyloxycarbonyl(lower)-alkylcarbamoyl (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyl dimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl).

Aromatic acyl is exemplified by aroyl optionally having suitable substituent(s) (e.g., nitro), such as benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl and the like; and arenesulfonyl optionally having one or more suitable substituent(s) (e.g., halogen), such as benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl and the like.

The aliphatic acyl substituted by aromatic group may be, for example, ar(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyloxy, trihalo(lower)alkyl and the like), wherein specific examples are phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl and the like.

Of the above-mentioned acyl, more preferable acyl includes C_1 - C_4 alkanoyl optionally having carboxy, cyclo(C_5 - C_6)alkyloxy(C_1 - C_4)alkanoyl having two (C_1 - C_4)alkyl in the cycloalkyl moiety, camphorsulfonyl, carboxy(C_1 - C_4)alkylcarbamoyl, tri(C_1 - C_4)alkylsilyl(C_1 - C_4)alkyloxycarbonyl(C_1 - C_4)alkylcarbamoyl, benzoyl optionally having 1 or 2 nitro groups, and benzenesulfonyl having halogen, phenyl(C_1 - C_4)alkanoyl having C_1 - C_4 alkyloxy and trihalo(C_1 - C_4)alkyl. Of these, most preferred are acetyl, carboxypropionyl, mentyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and the like.

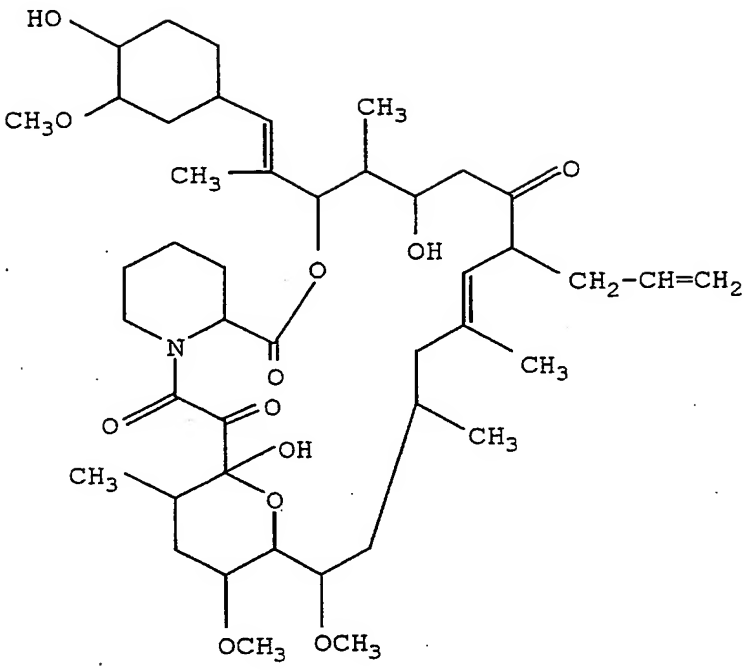
Preferable examples of the "heterocyclic group consisting of saturated or unsaturated 5 or 6-membered ring having nitrogen atom, sulfur atom and/or oxygen atom" are pyrolyl, tetrahydrofuryl and the like.

The "heteroaryl optionally having a suitable substituents" moiety of the "heteroaryloxy optionally having a suitable substituent" is that exemplified for R^1 of the compound of the formula I of EP-A-532088, with preference given to 1-hydroxyethylindol-5-yl. This publication is incorporated hereinto by reference.

The tricyclo compound (I) and a pharmaceutically acceptable salt thereof to be used in the present invention have superior IL-2 inhibitory action and immunosuppressive action, antibacterial action and other pharmacological activity, so that they are useful for the prophylaxis and treatment of rejection in organ or tissue transplantation, graft versus host reaction, autoimmune diseases, infectious diseases and the like, as noted, together with the production method thereof, in, for example, EP-A-184162, EP-A-323042, EP-A-423714, EP-A-

427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059 and the like, all of these publications are hereby incorporated by reference.

In particular, the compounds called FR900506 (=FK506), FR900520 (Ascomycin), FR900523 and FR900525 are produced by the genus *Streptomyces*, such as *Streptomyces tsukubaensis*, No. 9993 (depository: National Institute of Advanced Industrial Science and Technology, International Patent Organism Depositary, Central 6, 1-1 Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly: Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit: October 5, 1984, deposit number: FERM BP-927) or *Streptomyces hygroscopicus subsp. Yakushimaensis*, No. 7238 (depository: National Institute of Advanced Industrial Science and Technology, International Patent Organism Depositary, Central 6, 1-1 Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly: Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit: January 12, 1985, deposit number: FERM BP-928 (EP-A-0184162), and the compound of the following formula), FK506 (general name: Tacrolimus) is a representative compound.



Chemical name : 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

Of the tricyclo compounds (I), more preferred is a compound wherein adjacent pairs of R^3 and R^4, and R^5 and R^6 may each independently form another bond between carbon atoms binding with the members of each pairs;

R^8 and R^{23} each independently show hydrogen atom;

R^9 is hydroxy;

R^{10} is methyl, ethyl, propyl or allyl;

X is (hydrogen atom, hydrogen atom) or oxo;

Y is oxo;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{22} each independently show methyl;

R^{24} is 3-R^{20}-4-R^{21}-cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and

R^{21} is hydroxy,-OCN, alkyloxy, heteroaryloxy optionally having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired, or protected amino, and R^{26} is hydrogen atom or methyl), or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring; and

n is 1 or 2.

Particularly preferable tricyclo compound (I) include, besides FK506, Ascomycin derivatives such as halogenated derivative of 33-epi-chloro-33-desoxy Ascomycin described in Example 66a of EP-A-427,680 and the like.

Other preferable IL-2 inhibitors (macrolide compounds) include Rapamycin described in MERCK INDEX, 12 edition, No. 8288 and derivatives thereof. Preferable examples thereof include O-substituted derivative described at page 1 of WO95/16691, formula A, wherein the 40th hydroxy is $-OR_1$ (wherein R_1 is hydroxyalkyl, hydroalkyloxyalkyl, acylaminoalkyl or aminoalkyl), such as 40-O-(2-hydroxy)ethyl Rapamycin, 40-O-(3-hydroxy)propyl Rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl Rapamycin and 40-O-(2-acetaminoethyl)Rapamycin. These O-substituted derivatives can be produced by reacting, under appropriate conditions, Rapamycin (or dihydro or deoxo Rapamycin) and an organic radical bound with a leaving group (e.g., RX wherein R is an organic radical desirable as O-substituent, such as alkyl, allyl and benzyl moiety, and X is a leaving group such as $CCl_3C(NH)O$ and CF_3SO_3)). The conditions

are : when X is $CCl_3C(NH)O$, acidic or neutral conditions, such as in the presence of trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their corresponding pyridinium or substituted pyridinium salt, and when X is CF_3SO_3, in the presence of a base such as pyridine, substituted pyridine, diisopropylethylamine and pentamethylpiperidine. The most preferable Rapamycin derivative is 40-O-(2-hydroxy)ethyl Rapamycin as disclosed in WO94/09010, which is hereby incorporated into the specification by reference.

The pharmaceutically acceptable salt of tricyclo compound (I), Rapamycin and derivatives thereof are nontoxic and pharmaceutically acceptable conventional salts, which are exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

In the IL-2 inhibitor of the present invention, particularly macrolide compound, conformers and one or more pairs of stereoisomers such as optical isomers and geometric isomers, which are due to asymmetric carbon atom and double bond, may be included. Such conformers and isomers are also encompassed in the present invention. In addition, macrolide compounds can form solvates, which case is also encompassed in the present invention. Preferable solvate is exemplified by hydrates and ethanolates.

Other IL-2 inhibitors are known from MERCK INDEX, 12th ed., No. 2821, US Patent Nos. 4,117,118, 4,215,199, 4,288,431, 4,388,307, Helv. Chim. Acta, *60*, 1568 (1977) and *65*, 1655 (1982) and Transplant. Proc. *17*, 1362 (1985)

and the like. Specifically, they are cyclosporins such as cyclosporin A, B, C, D, E, F and G and derivatives thereof. Particularly preferred is cyclosporin A. These publications are hereby incorporated into the specification by reference.

The tricyclo compound (I), pharmaceutically acceptable salt thereof, cyclosporins and derivatives thereof can be classified as "IL-2 production inhibitor" that inhibits production of IL-2. Rapamycin and derivative thereof can be classified as "IL-2 signal transduction inhibitor" that inhibit transmission of IL-2 signal.

In the present invention, the allergic disease encompasses any reaction type of IgE dependent anaphylactic type (I type), cytotoxic type (II type), immune complex type (III type) and cellular immunity type (IV type), as classified by Coombs and Gell (1963) mentioned above. In particular, bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergy, drug allergy and the like classified under I type allergy are the suitable diseases to be targeted.

The treatment in the context of the present invention includes any management such as prevention, cure, alleviation of symptom, reduction of symptom, prevention of progression and the like.

By "for pre-administration" of the "pharmaceutical agent for pre-administration" and "pharmaceutical composition for pre-administration" of the present invention is meant administration in advance in a treatment method of allergic diseases, which comprises administering an IL-2 inhibitor to a subject in need of a treatment of allergic diseases for a given period of time

(i.e., leading period) and thereafter again administering an effective amount of an IL-2 inhibitor. In the present specification, an IL-2 inhibitor used for pre-administration is distinguished from an IL-2 inhibitor to be administered after the leading period for pre-administration, as an IL-2 inhibitor to be used for treatment of allergic disease (to be referred to simply as during treatment).

According to the present invention, by setting a leading period for pre-administration of an IL-2 inhibitor, the effect on the allergic diseases can be expressed in a remarkably enhanced manner. For example, since the period of onset and termination of seasonal allergic diseases are mostly determined, a leading period for pre-administration set before the probable season of the onset of the disease enables more effective treatment of the disease. In the present invention, therefore, seasonal allergic diseases such as seasonal allergic conjunctivitis and seasonal allergic rhinitis are among the suitable target diseases. In addition, by setting a leading period for pre-administration, treatment with an IL-2 inhibitor at lower concentrations or with less frequency of the instillation per day, when the allergic diseases can be treated, becomes attainable thereby decreasing the burden on the patient.

According to the present invention, the above-mentioned IL-2 inhibitor is administered in an effective amount for the treatment of allergic disease to a subject in need thereof, after the leading period for pre-administration.

The IL-2 inhibitor used in the present invention for pre-administration and/or treatment of allergic diseases can be used as a pharmaceutical agent for human and

animals, and can be administered systemically or locally by oral administration, intravenous administration (inclusive of transfusion), subcutaneous administration, rectal or virginal administration, administration to a local site of the eye (inclusive of eye ointment), administration to a local site of the nose (inclusive of spray). In consideration of systemic influence, significant expression of the effect and like, it is particularly preferably used in a form suitable for local administration.

The dosage form may be, for example, eye drop, eye ointment, nasal drop, spray, powder, granule, tablet, capsule, injection, ointment and the like, with particular preference given to eye drop, eye ointment, nasal drop, spray and the like. Such preparations can be produced according to conventional methods.

In the present invention, the leading period for pre-administration of an IL-2 inhibitor varies depending on the kind, age, body weight, condition to be treated, desired therapeutic effect, administration route and the like of the subject to be treated, such as human and animal. In general, the period is from 3 days to about 2 months, preferably from about 1 week to 1 month, which is determined as appropriate.

The dose of the IL-2 inhibitor during the leading period varies depending on the kind, age, body weight, condition to be treated, desired therapeutic effect, administration route, treatment period, leading period, and the like, with regard to the subject to be treated, such as human and animal. Generally, when it is administrated systemically, the dose is about 0.0001-1000 mg, preferably 0.001-500 mg, which is given in a single dose or 2 to 4 dividual doses a day or in a sustained

manner. When it is administered locally to the eye, a preparation containing the active ingredient in a proportion of 0.001 - 10.0 w/v%, preferably 0.005 - 5.0 w/v%, is applied several times a day per eye, preferably instilled or applied 1 to 6 times a day.

After the leading period for pre-administration of an IL-2 inhibitor, the dose and administration frequency of the IL-2 inhibitor for the treatment of the allergic disease are within the range specified above for the leading period. According to the present invention, the presence of the leading period enables reduction of the dose and administration frequency of the IL-2 inhibitor during the treatment.

The kind of the IL-2 inhibitor to be administered during the treatment is appropriately determined depending on the condition to be treated, desired therapeutic effect, administration route, treatment period, leading period and the like. It is preferable that the same IL-2 inhibitor administered during the leading period be used.

The present invention is explained in more detail in the following by way of Examples. The present invention is not limited by these Examples in any way.

Examples

Experimental Example 1

Method 1

Patients with allergic conjunctivitis (3 groups, 30 patients per group) were instilled with an antigen into the eye. Three minutes later, itchiness of the eye was evaluated in 9 levels (0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4), and the average value (base line group) of itchiness was determined. A specific antigen was determined for each patient. The antigen determined was the one against which the patient showed highest sensitivity in the preceding

confirmation test using 9 kinds of antigens (cat hair, cat dander, ragweed, birch, oak, maple, meadow fescue, rye, kentucky blue).

Method 2

At least one week was allowed to lapse from the test of Method 1, and FK506 eye drop (suspension) [0.03%, 0.06% or 0.1%] was instilled into the eye of the patients. At 8 hr after the instillation of the eye drop, the antigen was given. Three minutes later, itchiness of the eye was evaluated in the same manner as in Method 1, and the average value (without pre-administration) of itchiness was determined. In the group without pre-administration, the proportion (improvement rate) of the patients who showed at least 1 point lower itchiness than the base line itchiness was determined. The results are shown in Table 1.

Method 3

At least one week was allowed to lapse from the test of Method 2, and FK506 eye drop was instilled into the eye of the patients once a day for one week. At 16 hr after the last instillation of the eye drop, the antigen was given. Three minutes later, itchiness of the eye was evaluated in the same manner as in Method 1, and the average value (with pre-administration) of itchiness was determined. In the group with pre-administration, the proportion (improvement rate) of the patients who showed at least 1 point lower itchiness than the base line itchiness was determined. The results are shown in Table 1.

Table 1

Drug concentration	improvement (%) of group without pre-administration	improvement (%) of group with pre-administration
0.03%	25.93	61.54
0.06%	40.00	65.52
0.1%	56.67	72.41

INDUSTRIAL APPLICABILITY

From the above results, it is evident that the improvement effect on the itchiness can be strikingly enhanced by setting a leading period for pre-administration of FK506. For example, the improvement rate of the 0.03% concentration group with pre-administration was higher than that of the 0.1% concentration group without pre-administration. Hence, by setting a leading period for pre-administration, the allergic disease can be treated with a lower concentration of a medicament. In the comparison of 0.1% concentration groups, the improvement rate of the group with pre-administration after 16 hr was markedly higher than that of the group without pre-administration after 8 hr. Hence, by setting a leading period for pre-administration, the allergic disease can be treated with less frequency of the instillation.

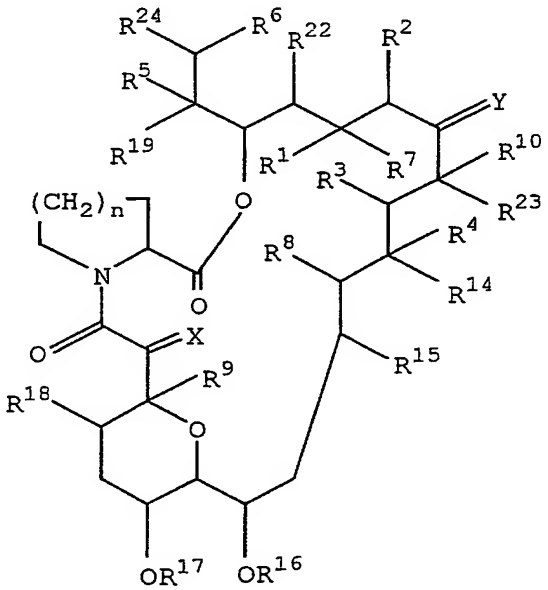
This application is based on application No. 60/331,722 filed in United States of America, the content of which is incorporated hereinto by reference.

CLAIMS

1. A pharmaceutical agent for pre-administration, which comprises an interleukin 2 inhibitor as an active ingredient, and which is used for treating an allergic disease, wherein the treatment includes a leading period for pre-administration of the interleukin 2 inhibitor to a subject in need of the treatment of allergic disease, and administration of an effective amount of an interleukin 2 inhibitor.

2. The pharmaceutical agent of claim 1, wherein the interleukin 2 inhibitor is a macrolide compound or a cyclosporin.

3. The pharmaceutical agent of claim 2, wherein the macrolide compound is a tricyclo compound (I) of the following formula;



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pairs;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2; and

Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical agent of claim 2 or claim 3, wherein the macrolide compound is FK506.

5. The pharmaceutical agent of claim 1, wherein the interleukin 2 inhibitor is a preparation for local administration.

6. The pharmaceutical agent of claim 5, wherein the local administration is administration to the eye or the nose.

7. The pharmaceutical agent of claim 1, wherein the allergic disease is allergic conjunctivitis.

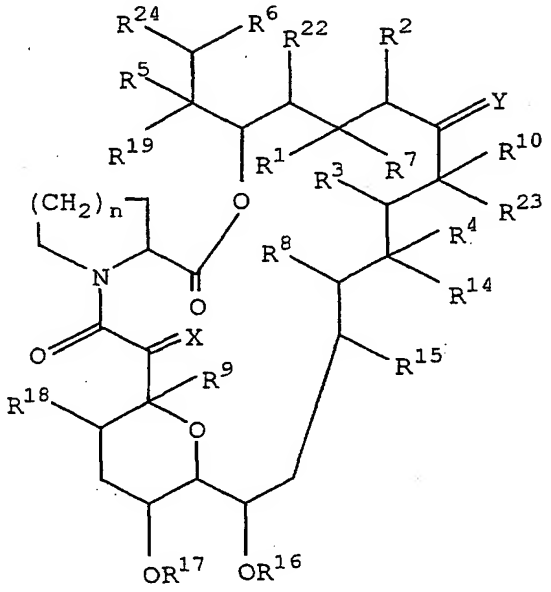
8. The pharmaceutical agent of claim 1, wherein the allergic disease is seasonal allergic disease.

9. The pharmaceutical agent of claim 8, wherein the seasonal allergic disease is seasonal allergic conjunctivitis.

10. A pharmaceutical composition for pre-administration, which comprises an interleukin 2 inhibitor as an active ingredient and a pharmaceutically acceptable carrier, and which is used for treating an allergic disease, wherein the treatment includes a leading period for pre-administration of the interleukin 2 inhibitor to a subject in need of the treatment of allergic disease, and administration of an effective amount of an interleukin 2 inhibitor.

11. The pharmaceutical composition of claim 10, wherein the interleukin 2 inhibitor is a macrolide compound or a cyclosporin.

12. The pharmaceutical composition of claim 11, wherein the macrolide compound is a tricyclo compound (I) of the following formula;



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pairs;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom,

hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2; and

Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition of claim 11 or claim 12, wherein the macrolide compound is FK506.

14. The pharmaceutical composition of claim 10, wherein the interleukin 2 inhibitor is a preparation for local administration.

15. The pharmaceutical composition of claim 14, wherein the local administration is administration to the eye or the nose.

16. The pharmaceutical composition of claim 10, wherein the allergic disease is allergic conjunctivitis.

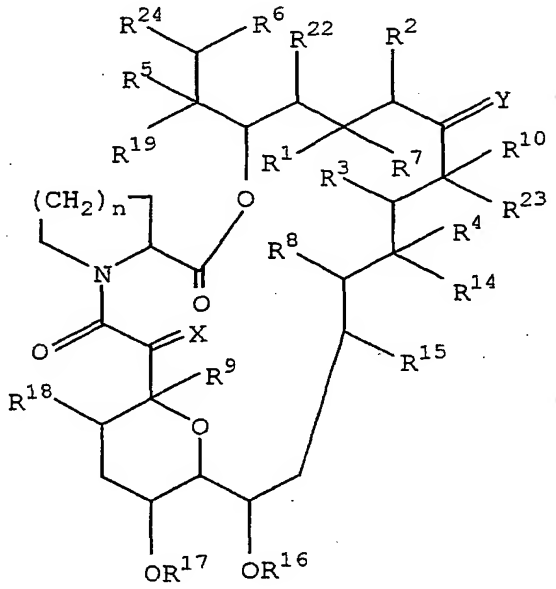
17. The pharmaceutical composition of claim 10, wherein the allergic disease is seasonal allergic disease.

18. The pharmaceutical composition of claim 17, wherein the seasonal allergic disease is seasonal allergic conjunctivitis.

19. A method for treating an allergic disease, which comprises pre-administering an interleukin 2 inhibitor for a leading period and then administering an effective amount of an interleukin 2 inhibitor to a subject in need of a treatment of an allergic disease.

20. The method of claim 19, wherein the interleukin 2 inhibitor is a macrolide compound or a cyclosporin.

21. The method of claim 20, wherein the macrolide compound is a tricyclo compound (I) of the following formula;



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pairs;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2; and

Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

22. The method of claim 20 or claim 21, wherein the macrolide compound is FK506.

23. The method of clam 19, wherein the interleukin 2 inhibitor is a preparation for local administration.

24. The method of clam 23, wherein the local administration is administration to the eye or to the nose.

25. The method of claim 19, wherein the allergic disease is allergic conjunctivitis.

26. The method of claim 19, wherein the allergic disease is seasonal allergic disease.

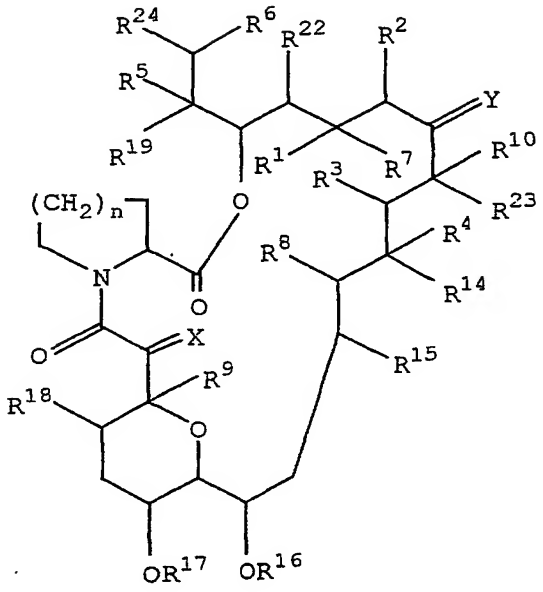
27. The method of claim 26, wherein the seasonal allergic disease is seasonal allergic conjunctivitis.

28. Use of an interleukin 2 inhibitor for the production of a pharmaceutical composition for pre-administration, which comprises the interleukin 2 inhibitor as an active ingredient and a pharmaceutically acceptable carrier, and which is used for treating an allergic disease, wherein the treatment includes a leading period for pre-administration of the interleukin 2 inhibitor to a subject in need of the treatment of allergic disease, and administration of an effective amount of an interleukin 2 inhibitor.

29. The use of claim 28, wherein the interleukin 2 inhibitor is a macrolide compound or a cyclosporin.

30. The use of claim 29, wherein the macrolide compound is

a tricyclo compound (I) of the following formula;



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pairs;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl,

aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2; and

Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

31. The use of claim 29 or claim 30, wherein the macrolide compound is FK506.

32. The use of claim 28, wherein the interleukin 2 inhibitor is a preparation for local administration.

33. The use of claim 32, wherein the administration is administration to the eye or the nose.

34. The use of claim 28, wherein the allergic disease is allergic conjunctivitis.

35. The use of claim 28, wherein the allergic disease is seasonal allergic disease.

36. The use of claim 35, wherein the seasonal allergic disease is seasonal allergic conjunctivitis.

37. A commercial package comprising the pharmaceutical composition of any of claims 10 to 18 and a written matter associated therewith, the written matter stating that the pharmaceutical composition can or should be used for pre-administration for treating allergic diseases, wherein the treatment includes a leading period for pre-administration of the interleukin 2 inhibitor to a subject in need of the treatment of allergic disease, and administration of an effective amount of an interleukin 2 inhibitor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted]02/12096

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/13 A61K31/436 A61P11/06 A61P27/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 19278 A (KURUME UNIVERSITY) 12 November 1992 (1992-11-12) cited in the application page 1, line 20 - line 29 page 2, line 1 - line 6 figure I page 8, line 26 -page 9, line 25 example 2 claims 1-9	1-37
X	"Protopic (tacrolimus)" FUJISAWA, 'Online! - December 2000 (2000-12) XP002230797 Retrieved from the Internet: <URL:http://www.protopic.com/img/protopic_ pi.pdf> 'retrieved on 2003-02-05! the whole document	1-23,26, 28-32, 35,37

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 2003	27/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Giacobbe, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 09010 A (SANDOZ AG ;SANDOZ AG (DE); SANDOZ LTD (CH); COTTENS SYLVAIN (CH);) 28 April 1994 (1994-04-28) cited in the application page 2, paragraph 2 -page 4, paragraph 2 ---	1-21, 28-30,37
X	US 4 215 199 A (HARRI EUGEN ET AL) 29 July 1980 (1980-07-29) cited in the application the whole document ---	1-18
X	US 5 912 253 A (COTTENS SYLVAIN ET AL) 15 June 1999 (1999-06-15) cited in the application page 1, line 1 -page 5, line 35 ---	1-18
X	US 4 288 431 A (TRABER RENE P ET AL) 8 September 1981 (1981-09-08) cited in the application the whole document ---	1-18
X	US 4 388 307 A (CAVANAK THOMAS) 14 June 1983 (1983-06-14) cited in the application the whole document -----	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/12096

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

- Present claims 1, 10, 19, 28 and 37 relate to a composition defined by reference to a desirable characteristic or property, namely the fact that the active component is an interleukin 2 inhibitor. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds comprised in the claimed compositions by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds claimed in claims 2 and 3.

- The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of claims 1-18, all referring to the first medical indication of known therapeutically active molecules. So many documents were retrieved that it is unlikely that any part of these claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these claims, a selection of the retrieved documents has been quoted.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted]02/12096

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9219278	A	12-11-1992	AT	198708 T	15-02-2001
			CA	2102241 A1	27-10-1992
			DE	69231644 D1	22-02-2001
			DE	69231644 T2	23-05-2001
			DK	581959 T3	29-01-2001
			EP	0581959 A1	09-02-1994
			ES	2154262 T3	01-04-2001
			GR	3035269 T3	30-04-2001
			WO	9219278 A1	12-11-1992
			JP	3158437 B2	23-04-2001
			JP	7500570 T	19-01-1995
			KR	237715 B1	01-02-2000
			US	5514686 A	07-05-1996
WO 9409010	A	28-04-1994	AT	173736 T	15-12-1998
			AU	676198 B2	06-03-1997
			AU	4819293 A	09-05-1994
			BR	1100353 A3	06-06-2000
			CA	2145383 A1	28-04-1994
			CZ	9500899 A3	13-09-1995
			DE	69322282 D1	07-01-1999
			DE	69322282 T2	12-05-1999
			DK	663916 T3	09-08-1999
			WO	9409010 A1	28-04-1994
			EP	0663916 A1	26-07-1995
			EP	0867438 A1	30-09-1998
			ES	2124793 T3	16-02-1999
			FI	951678 A	07-04-1995
			FI	20001943 A	04-09-2000
			HU	71232 A2	28-11-1995
			JP	11240884 A	07-09-1999
			JP	8502266 T	12-03-1996
			JP	3117462 B2	11-12-2000
			NO	951312 A	08-06-1995
			NZ	256026 A	27-08-1996
			PL	308268 A1	24-07-1995
			RO	114451 B1	30-04-1999
			RU	2143434 C1	27-12-1999
			SK	46595 A3	09-08-1995
			US	5665772 A	09-09-1997
			US	6440990 B1	27-08-2002
US 4215199	A	29-07-1980	NONE		
US 5912253	A	15-06-1999	AT	191218 T	15-04-2000
			AU	687491 B2	26-02-1998
			AU	1273995 A	03-07-1995
			BR	9408323 A	19-08-1997
			DE	69423781 D1	04-05-2000
			DE	69423781 T2	10-08-2000
			DK	734389 T3	21-08-2000
			EP	0734389 A1	02-10-1996
			FI	962487 A	14-06-1996
			GR	3033545 T3	29-09-2000
			JP	9506604 T	30-06-1997
			NO	962540 A	14-06-1996
			NZ	277498 A	25-03-1998
			SI	734389 T1	31-08-2000

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5912253 A		SK 78196 A3	05-02-1997
		CA 2174731 A1	22-06-1995
		CN 1137797 A ,B	11-12-1996
		CZ 9601757 A3	11-09-1996
		WO 9516691 A1	22-06-1995
		ES 2146741 T3	16-08-2000
		HU 74686 A2	28-01-1997
		PL 314238 A1	02-09-1996
		PT 734389 T	29-09-2000
		SG 64372 A1	27-04-1999
US 4288431 A	08-09-1981	CH 639961 A5	15-12-1983
		CH 642954 A5	15-05-1984
		CH 637124 A5	15-07-1983
		AT 381101 B	25-08-1986
		AT 14682 A	15-01-1986
		AU 530379 B2	14-07-1983
		AU 5191179 A	24-04-1980
		CA 1129359 A1	10-08-1982
		CY 1286 A	05-07-1985
		DE 2941080 A1	08-05-1980
		DK 428179 A ,B,	19-04-1980
		ES 485104 A1	16-05-1980
		FI 793142 A ,B,	19-04-1980
		FI 811005 A ,B,	01-04-1981
		FI 811006 A ,B,	01-04-1981
		FR 2439182 A1	16-05-1980
		GB 2033398 A ,B	21-05-1980
		HK 48685 A	28-06-1985
		IE 49084 B1	24-07-1985
		IL 58465 A	30-04-1982
		IT 1164109 B	08-04-1987
		KE 3517 A	19-04-1985
		MY 61885 A	31-12-1985
		NL 7907609 A	22-04-1980
		NZ 191865 A	31-05-1984
		PH 14086 A	10-02-1981
		PT 70324 A	01-11-1979
		SE 448386 B	16-02-1987
		SE 7908350 A	19-04-1980
		SG 14685 G	16-08-1985
		AT 381102 B	25-08-1986
		AT 14782 A	15-01-1986
		AT 375399 B	25-07-1984
		AT 672679 A	15-12-1983
		BE 879402 A1	15-04-1980
		JP 1493574 C	20-04-1989
		JP 55055150 A	22-04-1980
		JP 63040200 B	10-08-1988
		ZA 7905560 A	27-05-1981
US 4388307 A	14-06-1983	CH 636013 A5	13-05-1983
		AR 223667 A1	15-09-1981
		AT 375828 B	10-09-1984
		AT 163779 A	15-02-1984
		AU 528714 B2	12-05-1983
		AU 4486279 A	13-09-1979
		BE 874628 A1	05-09-1979

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted]02/12096

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4388307 A		CA 1139667 A1	18-01-1983
		CY 1285 A	05-07-1985
		DD 142149 A5	11-06-1980
		DE 2907460 A1	13-09-1979
		DK 86079 A ,B,	08-09-1979
		ES 478295 A1	16-05-1979
		FI 790640 A ,B,	08-09-1979
		FR 2419072 A1	05-10-1979
		GB 2015339 A ,B	12-09-1979
		HK 48585 A	28-06-1985
		HU 182920 B	28-03-1984
		IE 48016 B1	05-09-1984
		IL 56790 A	31-01-1982
		IT 1115038 B	03-02-1986
		JP 1404998 C	09-10-1987
		JP 54132223 A	15-10-1979
		JP 62007891 B	19-02-1987
		KE 3516 A	19-04-1985
		MY 13485 A	31-12-1985
		NL 7901703 A ,C	11-09-1979
		NO 790661 A ,B,	10-09-1979
		NZ 189819 A	31-05-1984
		PH 15159 A	24-08-1982
		PT 69309 A	01-04-1979
		SE 445174 B	09-06-1986
		SE 7901683 A	08-09-1979
		SG 14785 G	16-08-1985
		ZA 7901056 A	29-10-1980